PC Mini-Grids for Prediction of Viral RNA Structure and Evolution

Final Report – The Danish Agency for Science, Technology, and Innovation, grant no. #09-061856

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Background and Summary

This report describes the results of the PC Mini-Grids for Prediction of Viral RNA Structure and Evolution (MiniGrid) project granted by the Danish Agency for Science, Technology, and Innovation, grant no. #09-061856. This project aimed at designing a collaborative, peer-to-peer software architecture for distributed bioinformatics algorithms, which makes research into RNA-based diseases like HIV, SARS, and bird flu more efficient than with current approaches. The project was interdisciplinary and involved researchers from computer science, bioinformatics, molecular biology, and nanotechnology. The partners involved the IT University of Copenhagen (ITU), the Department of Molecular Biology (DMB), the interdisciplinary nano-science centre (iNANO) at the University of Aarhus (AU), and CLC bio A/S (CLC).

In summary, we conclude that the MiniGrid project has been very successful. It has meet all of its objectives and expected results, and has been able to pull additional resources into the project. From a research perspective, all of the original research objectives of the project have been met and published in 7 journal articles, 8 peer-reviewed conference papers[1], and 2 technical reports. From a business perspective, the research has been used to accelerate and improve bioinformatics algorithms in the CLC bio products, and the improved RNA folding algorithm PPfold has been released as plug-in to the CLC bio desktop software. Regarding research education, the original goal was to educate three PhD students as part of the project. One has graduated, one is defending this spring, and the last student is finishing end of 2013. From a research management point-of-view, the project has had a very efficient management structure, and no significant problems or issues have arisen. Lessons learned are being incorporated into the management of current research projects at ITU.

[1] To the reader coming from a scientific community outside of computer science, it should be noted that peer-reviewed conference papers are the main venue of publication within computer science, and is often much more competitive than journal publication.

Chapter 1

Scientific Results

The overall scientific objective of the PC Mini-Grids for Prediction of Viral RNA Structure and Evolution (Mini-Grid) project was to make theoretical and practical research into RNA-based diseases more efficient than with current, available methods. This is done by making bioinformatics software for theoretical analysis of RNA available for practical use in a biology laboratory.

In the MiniGrid project, the objective was to support biological research on viral RNA structure by utilizing local computing resources for distributed and collaborative bioinformatics computation and database search. More specifically, the project consisted of the following sub-objectives:

1. Create a distributed and robust peer-to-peer software architecture for collaborative, distributed computation running on ordinary personal computers. This architecture should be designed to be a general-purpose distribution platform for bioinformatics algorithms, which is used in this specific project to perform large-scale RNA structure prediction.

2. Redesign and implement existing RNA structure prediction algorithms to make them more suitable for parallelization and distribution, and use the enhanced calculation capacity to predict the global RNA structures of virus genomes of HIV, SARS and bird flu.

3. Experimental verification of the RNA structure predictions in the molecular biology laboratory. Novel RNA structures are synthesized and investigated by biochemical structure probing and analyzed at the single molecule level by Atomic Force Microscopy.

4. Design a good user interface for using the new grid technology and displaying the large amount of data in a simple manner. In addition, the platform should help users collaborate and hence help each other in the analysis of RNA sequences by allowing them to submit jobs to run on different machines and to divide the work among them.

Below we will elaborate more on the scientific results.

1.1 The Mini-Grid Framework

The Mini-Grid Framework has been designed, implemented and evaluated [6]. The Mini-Grid Framework is able to manage a peer-to-peer network infrastructure of end-user computers like desktop and laptop PCs, as well as more dedicated servers. The infrastructure runs cross-platform and supports Windows, Mac OS, and Linux. The framework supports task distribution, task auctioning, and task execution. In comparison to existing approaches to so-called "volunteer grid computing", the mini-grid enables a symmetric task distribution, an auction-based task scheduling, and context-aware task distribution based on the notion of “Contingency Management” [20, 7, 12]. The framework has been deployed in a test setup at DMB at AU and has been tested using the BLAST algorithm on up to 9 nodes. Furthermore, the framework has been tested with the PPfold algorithm [15] developed as part of the MiniGrid project. In these experiments, we found that the PPfold algorithm never ran slower on the Mini-Grid than when executing the same jobs locally, and in some cases significant speed-ups were obtained. Our results demonstrate more generally that context-awareness in ad-hoc network infrastructures enables an improved performance of complex algorithms [16].

1.2 RNA Structure Prediction

The PPfold algorithm was developed to reduce the long computation time when predicting RNA secondary structure based on evolutionary history. Parallelization of the inside-outside algorithm for the stochastic context-free grammar used in Pfold was achieved by the close analysis of the interdependencies to allow a subdivision of calculation tasks, as illustrated in Figure 1.1. In addition, the tree algorithms implemented in the evolutionary part of Pfold were also parallelized [15]. The algorithms were implemented in a flexible framework and fully integrated with execution in the Mini-Grid environment. PPfold is now also distributed by CLC bio as a free plugin to their Workbench products[1], and has also been used to predict the secondary structure of an entire HIV-1 genome (Figure 1.1).

In the newest version of PPfold, the original prediction models were extended with a flexible probabilistic model for incorporating experimental data, including data from the Selective 2-hydroxy acylation analyzed by primer extension (SHAPE) experiment [14]. With the increasing amounts of experimental probing data becoming available, this is an important extension to the algorithm in order to increase prediction accuracy. Previously, no other probabilistic methods for RNA secondary structure prediction existed that incorporated experimental data in this manner.

Lastly, our work with HIV-1 has shown that it is critical to address the issue of accuracy in the case of large-scale RNA secondary structure prediction. To this end, we have carried out a number of systematic studies in collaboration with colleagues at Georgia Institute of Technology and Oxford University, in which we investigated the correlations affecting prediction accuracy. Several peer-reviewed research papers have now been published with our recent results, including an evaluation of the factors affecting SHAPE-directed RNA secondary structure prediction accuracy [17], using information entropy as a predictor of structure accuracy and to characterize the RNA folding space [13], combining statistical alignment with RNA secondary structure prediction to reduce noise [5] and correlating alignment quality with prediction accuracy [4]. The application of these methods to predicting a high-reliability secondary structure for HIV-1 is ongoing.

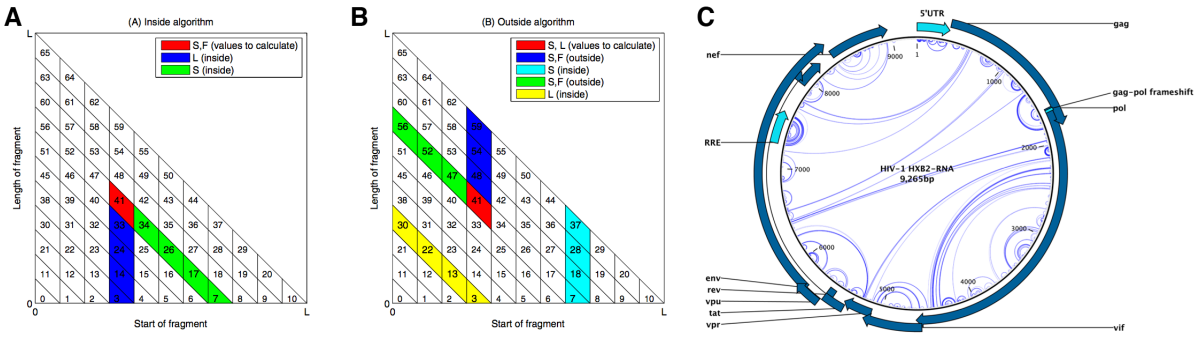

Figure 1.1: The PPfold algorithm. (A) Dependencies of the inside algorithm. (B) Dependencies of the the outside algorithm. (C) Circle diagram showing the predicted RNA structure of the HIV-1 RNA genome.

1.3 Experimental Verifications

The prediction of RNA secondary structure is limited by its simplified model and parameters and thus requires experimental verification [1]. To access whether the prediction is "interesting" a biologist will first look at the sequence covariation patterns, which indicates evolutionary conservation of the structural motif, and secondly at known biological sequence signals within the predicted structure, which indicates if the structure has a biological function in regulating these signals [2]. If promising, the RNA structure is isolated from its biological source and investigated further by biochemical and biophysical experiments to provide additional information about the 3-dimensional shape of the molecule and the possible biological function.

Atomic force microscopy has earlier been used to verify and study the function of predicted RNA structures in the HIV genome [3]. In this project we chose to use Small-Angle X-ray Scattering (SAXS) as the main method for investigating the 3-dimensional structure of predicted RNA structures, since this method is more native in investigating the structure in solution instead of on a surface. The 5' untranslated region of HIV-1 genome was

[1] `http://www.clcbio.com/clc-plugin/ppfold-plug-in/`

chosen as an example because it has been studied in the laboratory for several years. The RNA structure was prepared in large quantities and investigated for functional dimerization. Data was acquired for several different RNA samples at the local SAXS setup in the lab of Jan Skov Pedersen at Aarhus University. The predicted RNA model was used as the input for structural modeling by rigid body refinement and revealed an overall parallel orientation of the dimer molecule as well as finer structural features [4]. The study shows that combining RNA structure prediction with SAXS data results in a very detailed understanding of the 3D structure of RNA molecules.

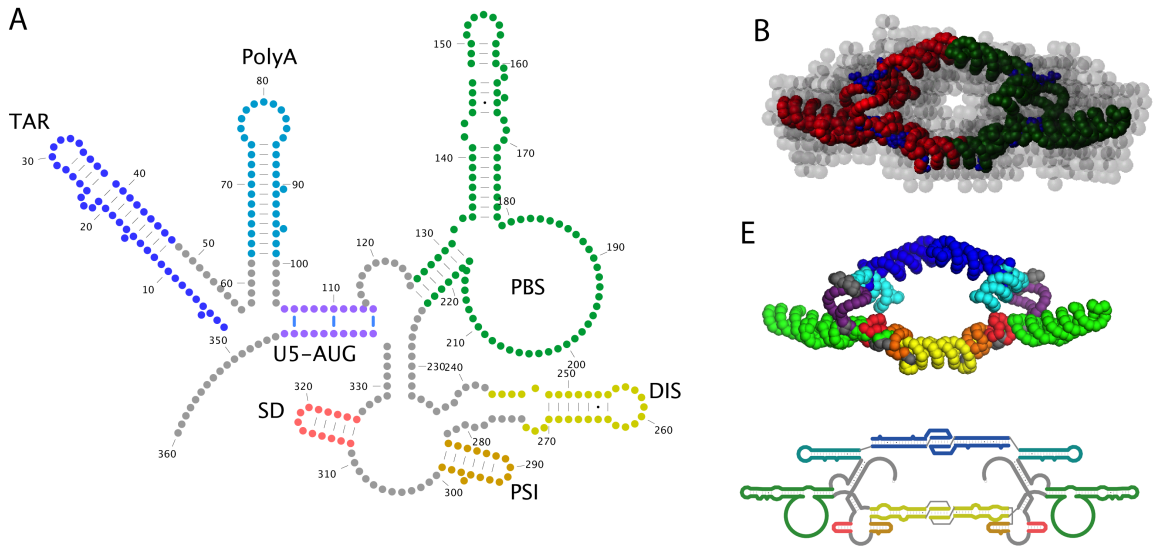

Figure 1.2: Study of the HIV leader RNA structure by Small-angle X-ray scattering.

1.4 Novel User Interfaces for Biology Work

A simple user-interface to submit and monitor distributed tasks in the mini-grid infrastructure has been implemented as part of the CLC bio Workbench. A more general system / user interface for providing "Grid Awareness" and foster collaboration within a biology laboratory has been designed [8, 10]. This uses large interactive displays, which are deployed, inside the different places in the biology laboratories, as shown in Figure 1.3. These displays allow users to maintain an awareness of the research taking place in the biology laboratory using the mini-grid, and allow for simple exchange of messages related to the different projects. The goal is to increase contribution to the grid by creating an awareness of its existence and benefit to research. Two large displays have been deployed and tested at the DMB at AU [9].

Figure 1.3: The GridOrbit public displays was deployed at two different places on the campus; across the corridor from the cafeteria (left), and next to the elevator in the local mail area (right).

In addition, the MiniGrid project also engaged in the design of a more complete vision of "Technologies for the Biology Laboratory of the Future". In a true interdisciplinary design process, we designed the eLabBench, which is an interactive laboratory workbench that allows biologists to access digital material and computational resources directly on the physical lab bench [19]. Figure 1.4 shows the eLabBench in use. The eLabBench was deployed for real use at DMB at AU for several months and has attracted quite some interests both from the research community [19, 18, 11] as well as from the public press. The eLabBench paper [19] won the best paper award at the 2011 International Conference on Interactive Tabletop and Surfaces (ITS) and has been features in news articles in the AU Press, Version2, Aarhus Stiftstidende, and others.

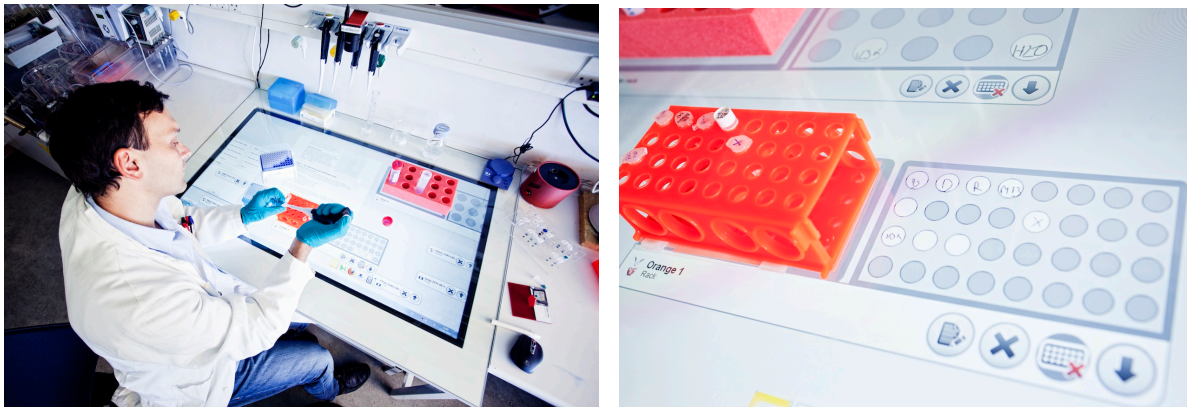

Figure 1.4: The eLabBench as deployed and in use at DMB at AU (left). The eLabBench provides access to digital material and integrates physical material like test tubes with the workbench (right).

In conclusion, from a research perspective, the MiniGrid project has been very successful and have meet all of its original goals. Moreover the design of the eLabBench that ties the vision of the computational future of laboratory work together has been designed, implemented, and deployed as part of this project. As can be seen from the reference list, the project has had significant impact in terms of publications in high-ranked venues, including top-tier journal on biology, nanotechnology, bioinformatics, distributed grid computing, interactive tabletop technology, and human-computer interaction.

Chapter 2

Business and Societal Results

In general, the project has developed methods for distribution of computationally complex bioinformatics algorithms. From a *business perspective*, these methods have been used to accelerate and improve the RNA folding algorithm Pfold leading to a parallelized version (the PPfold algorithm). As such, an important applied result of the project is that CLC bio has obtained significant experience in the area of parallelization and optimization of bioinformatics algorithms. Specifically, the improved RNA folding algorithm PPfold has been released as plug-in to the CLC bio desktop software[1]. It is planned that this accelerated PPfold algorithm will be implemented as a plug-in to the CLC bio server technology, which will significantly enhance the software platform.

Moreover, the close cooperation between biologists from AU and computer scientists form ITU has improved the CLC bio Software Development Kit. This close collaboration has provided CLC bio with a much better understanding of the complexity of distributing computational heavy jobs, which is now being used in the further research and development (R&D) at CLC bio. CLC bio is now a very successful company. Total revenue 2012 was USD 12.0 million and 98% of this was export. Hence, as a R&D-based company focusing solely on bioinformatics tools for advance scientific companies and institutions, CLC bio is very successful. The MiniGrid project has been part of this R&D effort, researching how to handle and execute computational complex algorithms. This has been very valuable research and insight for CLC bio.

The so-called "Rabbit" [11], which is a device for integrating physical material used on the eLabBench with the digital material stored in the eLabBench, has been subject for a patent application. A patent agency helped us form a patent application and it was submitted for database screening. The result of the screening was that the invention was novel and could be patented. However, ITU decided that they would not pursue this patent, and the researchers declined to do so as well.

From a *societal perspective*, the MiniGrid project has been widely disseminated at important venues. Here is a list of the most influential ones.

- The Danish IT online magazine Version2 brought an article on the eLabBench[2].
- The Faculty of Science and Technology at the University of Aarhus has made a story on the deployment of the eLabBench at the Micro-Biology lab[3].
- The story on the eLabBench was also brought in videnskab.dk[4].

Finally, the MiniGrid has been published on several web sites, including:

- At the Pervasive Interaction Technology Laboratory (PIT Lab) homepage[5].
- At the homepage of the IT University of Copenhagen[6]

[1] http://www.clcbio.com/clc-plugin/ppfold-plug-in/
[2] http://www.version2.dk/artikel/digital-revolution-i-laboratoriet-46-touch-skaerm-med-rfid-laeser-og-objekt
[3] http://scitech.au.dk/aktuelt/nyheder/vis/artikel/verdens-foerste-digitale-laboratoriebord-taget-i-brug/
[4] http://videnskab.dk/teknologi/se-fremtidens-vilde-laboratorium
[5] http://pitlab.itu.dk/research/project/collaborative-mini-grid
[6] http://www.itu.dk/da/Presse/Pressemeddelelser/elabbench

Chapter 3

Research Education

The original project application applied for three PhD scholarships, which has been partly funded from the grant and partly by the University of Aarhus and the IT University of Copenhagen. All of these students have successfully handed in their thesis and has, or is shortly going to, defend their thesis. The students and their thesis abstract are;

Neelanarayanan Venkataraman – *The Mini-Grid Framework: Application Programming Support for Ad hoc Volunteer Grids*. March 2011. IT University of Copenhagen.

Abstract: To harvest idle, unused computational resources in networked environments, researchers have proposed different architectures for desktop grid infrastructure. However, most of the existing research work focus on centralized approach. In this thesis, we present the development and deployment of one such infrastructure, called the Mini-Grid Framework for resource management in ad hoc grids using market-based scheduling and context-based resource and application modeling. The framework proposes peer-to-peer architecture that supports several futures: ease of deployment, decentralized task distribution, small scale ad hoc grid formation, and symmetric resource. Furthermore, users can model and specify non-performance based parameters that influence resource allocation.

We evaluated the framework through simulation experiments at the IT University of Copenhagen (ITU), as well as a pilot deployment at the Interdisciplinary Nano-science Center (iNano), Aarhus University. For the simulation experiments we used an application that calculates prime numbers between a given range, and another application that searches for a key in a large data set. In the simulation experiments, we studied the technical performance and overhead of the Mini-Grid Framework and compared its performance with other relevant systems. For the pilot deployment, we have integrated a parallelized version of the Basic Local Alignment Search Tool (BLAST) algorithm and the RNA secondary structure prediction algorithm developed by iNano research center with the Mini-Grid Framework. These algorithms have been developed on top of our framework through an integration of the framework with the CLC bio Workbench, a software suite for bioinformatics algorithms. The pilot deployment studied the resource participation, the deployment efforts needed, and the performance of the framework in a real grid environment.

The main contribution of this thesis are: i) modeling entities such as resources and applications using their context, ii) the context-based auction strategy for dynamic task distribution, iii) scheduling through application specific quality parameters, iv) the definition of an extensible API for ad hoc grid formation and v) enabling symmetric resource participation.

Juan David Hincapié-Ramos – *Using Infrastructure Awareness to Support the Recruitment of Volunteer Computing Participants*. August 2011. IT University of Copenhagen.

Abstract: The Mini-Grid is a volunteer computing infrastructure that gathers computational power from multiple participants and uses it to execute bioinformatics algorithms. The Mini-Grid is an instance of a larger set of systems that we call participative computational infrastructures (PCI). PCIs depend on their participants to provide a service, with every instance of the system executing similar tasks and collaborating with others. Participants to these infrastructures come together to contribute resources like computational power, storage capacity, network connectivity and human reasoning skills.

While plenty of research has focused on the technical aspect of these infrastructures (task parallelization, distribution, robustness, and security), the participative aspect, which deals with how to recruit and maintain participants, has been largely overlooked. Despite the multiple experiences with volunteer computing projects, only a few researchers have looked into the motivational factors affecting the enrollment and permanence of participants. This dissertation studies participation from the broader context of the relationship between users and infrastructures in the field of Human-Computer Interaction (HCI), and argues that participative computational infrastructures face a fundamental recruitment challenge derived from their being "invisible" computational systems.

To counter this challenge this dissertation proposes the notion of Infrastructure Awareness: a feedback mechanism on the state of, and changes in, the properties of computational infrastructures provided in the periphery of the user's attention, and supporting gradual disclosure of detailed information on userÕs request. Working with users of the Mini-Grid, this thesis shows the design process of two infrastructure awareness systems aimed at supporting the recruitment of participants, the implementation of one possible technical strategy, and an in-the-wild evaluation. The thesis finalizes with a discussion of the results and implications of infrastructure awareness for participative and other computational infrastructures.

Zsuzsanna Sükösd – *Prediction of viral RNA secondary structure*. Thesis to be handed in August 2013. University of Aarhus. Interdisciplinary Nanoscience Center and Bioinformatics Research Centre.

Abstract: The prediction of the structure of large RNAs, such as the genome of the HIV virus, remains a particular challenge in bioinformatics, due to the computational complexity and low levels of accuracy of state-of-the-art algorithms. This dissertation presents several contributions in this field, including theoretical developments and the practical application of the theory to real-world data. To address the performance issues arising for large amounts of data, the PPfold algorithm was developed, which is a parallelized and improved version of the pfold algorithm for RNA secondary structure prediction, fully integrated into both the CLC Workbenches and the Mini-Grid. To further enhance the usefulness of this algorithm, the underlying model and its practical implementation were extended with a probabilistic framework for incorporating experimental data, such as from RNA probing experiments, into structure predictions. Nevertheless, prediction quality remained an important issue, as we observed that neither stochastic nor thermodynamic prediction algorithms are robust against poor quality in the input data. This highlighted the need to quantify input data quality and estimate its effect structure prediction accuracy. Key contributions in this regard have been a systematic study of SHAPE-directed RNA secondary structure prediction, as well as the application of information entropy to characterize RNA folding space. Finally, we have applied these research results in the prediction of a phylogenetically and experimentally supported secondary structure for the HIV-1 virus genome.

In addition, two post-docs have been closely associated with the project:

Aurelien Tabard – *Project management, Supervision, Infrastructure Awareness, and the eLabBench.* Pervasive Interaction Technology Laboratory, IT University of Copenhagen

Ebbe Sloth Andersen – *Project management, Supervision, and verification of RNA structures by biophysical methods*. Department of Molecular Biology and Genetics, and Interdisciplinary Nano-science Center, Aarhus University.

Chapter 4

Project Management and Cooperation

The steering group for the project has been:

- Jørgen Staunstrup, ITU
- Jakob E. Bardram, ITU
- Jørgen Kjems, AU
- Thomas Knudsen, CLC bio

Daily project management has been done by Jakob E. Bardram (ITU) and Ebbe S. Andersen (AU). This management setup has been really strong in the project, and have been able to handle all project related issues as they arose.

Cooperation across institutions have been a huge success. Researchers have been working closely together (as reflected in the research results listed above), and the researchers have spend a lot of time at both research institutions (the University of Aarhus and at the IT University of Copenhagen) and at CLC bio. Frequent trips with DSB to/from Copenhagen/Aarhus has been made.

As can also be seen from the research results described in chapter 1, the work and research done in this project have been highly *interdisciplinary*. Researchers with a background in mathematics, bioinformatics, biology, computer science, and design have worked closely together to design and implements everything from high-performance algorithms, to distributed grid computing architecture and to advanced visualization and interaction techniques for the future of the biology laboratory. Special emphasis can be put on the eLabBench, which were designed in an truly interdisciplinary design process involving everybody in the project [8].

Internationally the project members have been cooperating with a number of top-tier institutions. Juan David Hincapié-Ramos spend 6 month at the University of California at Irvine (UCI) researching the concept and technology of infrastructure awareness. Neelanarayanan Venkataraman spend 4 month at the University of Lancaster, UK while doing research on distributed grid computing in a pervasive computing context. Finally, Zsuzsanna Sükösd has spent 5 months at the School of Mathematics, Georgia Institute of Tehcnology (Atlanta, USA), researching the factors affecting SHAPE-directed RNA secondary structure prediction accuracy. She has also continued fruitful collaboration with colleagues at Oxford University, UK, working on evaluating and improving evolutionary methods used in RNA secondary structure prediction. All in all, the international collaboration has been quite influential and beneficial to this project.

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